Secondary sclerosing cholangitis as cause of persistent jaundice in patients with severe COVID-19

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/LIV.14971

KPB, PDWG, SB. Drafting of the article: BMo, CJ, DL, SB. Critical revision of the article for important intellectual content: BMü, CSR, EMM, GB, MH. Final approval of the article: all authors.

Word count main body of manuscript: 3'778

Number of figures and tables: 3 tables, 5 Figures

Summary

Background & Aims: Little is known about cholestasis including its most severe variant secondary sclerosing cholangitis (SSC), in critically ill patients with coronavirus disease 19 (COVID-19). In this study we analyzed the occurrence of cholestatic liver injury and SSC, including clinical, serological, radiological and histopathological findings.

Methods: We conducted a retrospective single-center analysis of all consecutive patients admitted to the intensive care unit (ICU) due to severe COVID-19 at the University Hospital Zurich to describe cholestatic injury in these patients. The findings were compared to a retrospective cohort of patients with severe influenza A

Results: 34 patients with severe COVID-19 admitted to the ICU were included. 14 patients (41%) had no cholestasis (group 0), 11 patients (32%, group 1) developed mild and 9 patients (27%, group 2) severe cholestasis. Patients in group 2 had a more complicated disease course indicated by significantly longer ICU stay (median 51 days IQR 25-86.5) than the other groups (group 0 median 9.5 days IQR 3.8-18.3 p=0.001 and group 1 median 16 days IQR 8-30 p< 0.05 respectively). Four patients in group 2 developed SSC compared to none in the influenza A cohort. The available histopathological findings suggest an ischemic damage to the perihilar bile ducts.

Conclusions: The development of SSC represents an important complication of critically ill COVID-19 patients and needs to be considered in the diagnostic work up in prolonged cholestasis. The occurrence of SSC is of interest in the ongoing pandemic since it is associated with considerable morbidity and mortality.

Word count: 248/250

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Lay Summary:

Data on severe affection of bile ducts in COVID-19 patients are scarce. Herein, we describe the occurrence of bile duct injury in a cohort of 34 critically ill COVID-19 patients. In 20 patients, evidence of bile duct injury was found thereof four developed a chronic disorder of the bile ducts, the so called secondary sclerosing cholangitis. Such bile duct injury was not detected in a comparative cohort of critically ill influenza A patients. The occurrence of this complication is of interest since the development of secondary cholangitis may be more frequently observed in COVID-19 patients compared to other critical illnesses, leading to a significant number of patients with a chronic, difficult to treat disorder of the bile ducts.

Introduction

The severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), a novel pathogen causing coronavirus disease 2019 (COVID-19), has spread globally, causing an ongoing pandemic with more than 1'000'000 deaths so far[1]. Most COVID-19 patients present with mild cold- and flu-like symptoms including fever (88.7%) and cough (67.8%), anticipating a good prognosis[2]. Patients with older age and/or underlying conditions, however, are at increased risk for the development of severe pneumonia, resulting in the acute respiratory distress syndrome (ARDS) and multi-organ failure[3]. Even though the main health care focus lies in the severe pulmonary affections of the disease, it has become evident that COVID-19 can affect multiple organ systems including the liver. Being still matter of debate, the etiology of the liver injury in these patients may be multifactorial either directly, as the ACE2 receptor is abundantly expressed in cholangiocytes or indirectly as result of a severe inflammatory response/sepsis, hypoxic or drug induced liver injury[4,5,6]. Several studies demonstrated that elevations of liver enzymes are observed in up to 50% of the patients[2,7-9].

Within the spectrum of liver injury in COVID-19 patients, cholestasis was considered to be a rare event. Higher gamma-glutamyl-transferase (GGT) levels as well as elevated bilirubin were reported be associated with disease severity[2,10]. However, in a recent meta-analysis elevations of alkaline phosphatase elevation was reported in 6.1% and GGT elevation in 21.1%[11]. Bile duct injury in patients with severe COVID-19 could be a result of hypoxia and severe SIRS or potentially by direct infection of cholangiocytes.

The development of secondary sclerosing cholangitis (SSC) has been described in ICU survivors in several case series as a late complication of different underlying diseases requiring long term ICU care and is called and is named sclerosing cholangitis in critically ill patients (SC-CIP)[3,12,13]. SC-CIP is a chronic cholestatic liver disease that is observed as a rare complication of critically ill patients resembling the primary sclerosing cholangitis which can proceed to biliary cirrhosis[13]. The etiology of SC-CIP is incompletely understood. However, ischemic injury to the biliary tree with the formation of biliary casts, frequently infected with multiresistant bacteria appear to be the major pathogenic determinants[12]. Since ARDS in combination with septic shock is observed in a significant proportion of patients with severe COVID-19, SC-CIP may be recognized as a late sequela of the COVID-19 pandemic[14]. In fact, several case reports have described the occurrence SC-CIP as complication of severe COVID-19[15-17].

In this retrospective single center cohort study, we aim to describe the pattern and severity of cholestatic liver injury including the development of SC-CIP in critically ill COVID-19 patients. Because little is known on the occurrence of SC-CIP as a complication of severe viral infection with ARDS, we compare the degree of cholestasis in COVID-19 patients to a cohort of critically ill influenza A patients.

Methods

Study design: We conducted a retrospective single center cohort study of all consecutive, non-selected patients admitted to the ICU due to COVID-19 at the University Hospital Zurich between March and June 2020. The study was approved by the local ethics committee (Kantonale Ethikkommission Zürich, ID 2020-01656) and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. All patients admitted to the ICU due to severe COVID-19 during the study period were evaluated for eligibility. Only patients with existing written consent for further use of their health-related clinical data were included. Patients with documented refusal, missing written consent and missing liver function tests were excluded from analysis. All patient characteristics, disease- and treatment-related data, as well as laboratory values within this period were retrieved from the patients' medical record following a predefined protocol.

Characterisation of comparative influenza A cohort: 34 consecutive, critically ill influenza A patients with acute hypoxemic respiratory failure treated in the ICU of the University Hospital Zurich between February 2016 and February 2020 with existing written consent for further use of their health-related clinical data were analyzed. Patient characteristics, disease- and treatment-related data, as well as laboratory values within this period were also retrieved from the patients' medical record following a predefined protocol.

Definitions: Mild cholestasis was defined as an alkaline phosphatase (ALP) level of ≥1.5x the upper limit of normal (ULN) and GGT level of ≥3x ULN (group 1) as suggested by the European Association for the Study of the Liver[18]. Patients with additional total bilirubin of ≥2x ULN, defining liver dysfunction in drug induced liver injury[19] were considered to have severe cholestasis (group 2) as suggested in a previous work by de Tymowski et al. evaluating burn-associated cholestasis in critically ill patients[20]. All other patients were allocated to group 0 (without cholestasis). We defined COVID-19 associated SC-CIP as a cholestatic liver injury with the typical radiological findings in MRCP (as described below) in patients with severe SARS-CoV-2 infection admitted to the ICU, who had no evidence of a cholestatic liver disease prior to the current hospital admission.

Objectives: To describe the frequency and severity of cholestatic liver injury in critically ill COVID-19 patients and compare it to a cohort of critically ill influenza A patients.

Radiology: Radiology reports of abdominal imaging (abdominal ultrasound, computed tomography or magnetic resonance cholangiography) were reviewed for evidence of obstructive cholestasis or SC-CIP wherever available. All images of group 2 were additionally reviewed by an expert radiologist (CSR) in GI imaging to confirm diagnosis of SC-CIP and exclude obstructive cholestasis. The biliary tract was preferably imaged with magnetic resonance MRCP. On MRCP, SC-CIP was suspected in case of irregularities of the bile ducts with dilatations and strictures, if other causes of biliary dilatation were excluded. If computed tomography (CT) was performed a non-enhanced (in case of severe renal insufficiency) or portal venous phase of the abdomen was acquired to exclude biliary obstruction.

Histopathology: All tissue samples (two liver biopsies as well as liver tissue from four autopsy cases) were processed according to standard histological methods, i.e. formalin-fixed, paraffin-embedded and stained with hematoxylin & eosin (H&E). Additionally, Sirius red and/or elastic van Gieson (EVG) stainings to highlight the connective tissue structures as well as immunohistochemistry to highlight epithelial structures of bile ducts were performed. For immunohistochemistry standard procedures were applied using the VentanaBenchMark automated staining system for CK7 antibody (clone OV-TL 12/30; Dako, USA). Histological slides were evaluated by two experienced liver pathologists (DL and EMM).

Statistical analysis: Distribution of the data was analyzed by the Kolmogorov normality test for continuous variables. Continuous variables are expressed as median and interquartile range (IQR). Categorical variables were expressed as counts and percentages. Statistical analysis was performed by Mann-Whitney U test, Kruskal-Wallis test, Fisher's exact test and Chi-Square test as appropriate. All statistical analyses were performed using IBM® SPSS® Statistics Version 26 (International Business Machines Corporation - IBM, Armonk, NY USA) and the R environment for statistical computing (R Foundation for Statistical Computing, Vienna, Austria; Version 3.6.1.).

Results

Patient characteristics: 44 patients were admitted to the ICU due to COVID-19 during the observation period, thereof 10 were excluded due to missing informed consent for further use of their health-related clinical data (Figure 1). Finally, 34 COVID-19 patients were eligible for analysis in this study. There was no relevant difference of comorbidities among the different cholestasis groups (Table 1) apart from diabetes mellitus. The incidence of Diabetes was highest in the group with severe cholestasis but also prominent in the group without cholestasis (78% in group 2 vs. 50% in group 0 and 9% in group 1; p=0.228 and p=0.005 respectively). A total of 20 patients (59%) developed cholestasis during hospital stay, thereof nine patients (27%) had severe intrahepatic cholestasis (Table 1, Figure 1). None of these patients showed clinical or radiological evidence of obstructive cholestasis. Patients with severe cholestasis (group 2) had a significant longer ICU stay than patients of group 0 and 1, but at ICU admission disease severity was not different (measured by SAPS II Score; Table 1, Figure 2). Furthermore, patients with severe cholestasis needed higher levels of supportive care during ICU stay including renal replacement treatment, extracorporal membrane oxygenation (ECMO) and proning compared to patients without cholestasis (Figure 2). All patients in group 1 and 2 received Ketamine.

Comparison with the influenza A cohort: All COVID-19 patients were compared to 34 consecutive, critically ill influenza A patients (Figure 1). In the COVID-19 cohort, there were significantly more male patients (Table 2). According to SAPS II and SOFA score patients with influenza A were significantly sicker compared to the patients with COVID-19. However, length of hospital stay was significantly longer in the COVID-19 cohort. With respect to comorbidities, arterial hypertension was more prevalent in the COVID-19 group. COVID-19 patients received significantly more often respiratory support using prone positioning. The two cohorts did not differ in frequency of vasopressor use (Table 2). No Ketamine was used in the influenza A cohort.

Liver injury in the COVID-19 cohort: None of the included individuals had a history of preexisting chronic liver disease. There was no difference in liver function tests at admission among different cholestasis subgroups, apart from significantly increased AST in group 1 compared to group 0 and 2 (1.9 [0.9-2.1] x ULN vs. 0.9 [0.6-1.1] and 0.9 [0.7-1.0] respectively; *p* = 0.007 and 0.039 respectively, Table 1). Of interest, four patients with severe cholestasis (group 2) revealing persistently elevated cholestasis parameters developed SC-CIP (diagnosed by MRCP, two of them additionally received a liver biopsy - see below and Table 3). One of these patients was evaluated and is currently listed for liver transplantation due to persistent jaundice and pruritus, two died after ICU discharge. Regardless of the degree of cholestasis, most patients (six of seven patients; 86%) with markedly elevated ALT (>10x ULN) during ICU stay showed an unfavorable outcome either developing SC-CIP and/or dying (Figure 3).

Liver injury in the Influenza A cohort: Four patients in this comparative cohort had a history of chronic liver disease. Furthermore, patients with influenza A presented with significantly higher AST and AP levels at admission to ICU compared to the COVID-19 patients (Table 2). In the influenza cohort, only two patients

developed severe cholestasis but none of these patients was diagnosed with SC-CIP during follow up (Figure 1, Table 2). Cholestasis parameters spontaneously declined in both patients.

UDCA treatment: All 4 patients with SC-CIP received UDCA treatment (Table 3). Of the two patients who died, one patient had decreasing serological parameter of cholestasis before death, the other patient did not show any improvement. Both of the two patients with SC-CIP who are alive reported a significant improvement of pruritus, the patient on the waiting list for liver transplantation showed a decline of laboratory markers of cholestasis but is still deeply jaundiced. In the other patient, no effect on laboratory markers was detectable, moreover transient elastography increased over time.

Follow up of patients with COVID-19 infection: Follow up data was available up to 10 months after diagnosis of COVID-19 (median 4.7, range 1 – 11). Ten patients (29%) died during the follow-up time (Table 1). Mortality was significantly higher in the group 2 compared to group 0 (65 vs. 7%, p=0.018). However, there was no difference between the other groups.

One patient (group 2) deceased 6.5 month after COVID-19 diagnosis due to several complications after prolonged and repetitive stays on the ICU. This patient had moderate cholestasis (GGT 626 U/l with normal bilirubin levels and unremarkable liver imaging). Three patients of group 1 presented with mild cholestasis during follow up consultations, whereas the remaining showed normal LFTs. One patient was lost of follow up. Taken together, there is no evidence that additional patients developed SSC during the follow up period.

Radiological findings: All patients of group 2 and most patients of group 1 (9 of 12, 78%) had at least one abdominal imaging study to exclude obstruction of the biliary tract. In group 1 eight patients had at least one CT scan and one patient had an abdominal ultrasound, all negative for biliary obstruction. In group 2, four patients had a MRCP, two patients an abdominal ultrasound and CT, two additional patients only an abdominal ultrasound. In all four patients undergoing MRCP, imaging confirmed diagnosis of SC-CIP. In none of the eight patients of group 2 there was any evidence for biliary obstruction.

Histopathological findings: In two of the four patients who developed SC-CIP a liver biopsy was performed (55 and 67 days after COVID-19 was diagnosed). Histopathological findings in both patients were almost identical and included portal edema, mixed portal inflammation and pronounced bile duct damage with ductular reaction as well as lobular bile infarcts and severe hepatocellular, canalicular and focally ductular cholestasis (Fig. 4, A-C). There was some degree of pericellular fibrosis around portal tracts and central veins, but no fibrotic septa or cirrhosis (Fig. 4, D).

In four of the seven deceased patients an autopsy was performed (one patient from cholestasis group 2 and three patients from cholestasis group 1), and thus, liver tissues - including hilar structures - were available for histopathological evaluation. Time between death and autopsy was 22 hours in cholestasis group 2 and 1 day 5 hours, 2 days 6 hours and 2 days 8 hours in cholestasis group 1. In the patient in cholestasis group 2 transmural necrosis was present in some large and medium sized perihilar bile ducts

(Figure 4, E), whereas in two of the three patients in cholestasis group 1 those bile ducts showed mild to moderate epithelial damage and detachment but viable walls (Figure 4, F). The third patient in group 1 presented with acute abdomen and rising bilirubin levels one day before death. The autopsy indeed revealed not only mesenteric ischemia, but also complete transmural necrosis of perihilar bile ducts like the patient in cholestasis group 2. While mild damage and inflammation of the small peripheral bile ducts was observed in both groups, hepatocellular, canalicular and ductular cholestasis, as well as necrosis of peribiliary arterioles were detected only in the patients with transmural bile duct necrosis. In none of the analyzed samples, unequivocal endothelialitis and/or thrombi were evident in the peribiliary vessels. However, in the patient with mesenteric ischemia, focal endothelialitis was found in a peripheral portal vein branch, associated with intraluminal thrombotic material. In the patient in cholestasis group 2, portal vein thrombi were observed even without evident endothelialitis. A further important histopathological finding in the patients with transmural bile duct necrosis was hepatocyte necrosis. Whereas the patient with mesenteric ischemia had only recent pericentral necrosis, the patient in cholestasis group 2 additionally showed several up to a few centimeters large fresh parenchymal infarcts.

Discussion

In this retrospective cohort study of 34 consecutive unselected patients admitted to the ICU due to severe COVID-19 a high proportion developed cholestatic liver injury. Of note, four patients (12%) in the COVID-19 cohort developed SC-CIP compared to none in the influenza A cohort with severe ARDS.

Up to date, SC-CIP has been described in several cohort studies from different centers[3,12]. However, the prevalence of SC-CIP is unknown yet indirect evidence suggests that it is rare sequelae of critical illness. A recent review summarizing published case series of SC-CIP since 2001 indicated approximately 200 cases in total [21]. In contrast, in our cohort a relatively high proportion of COVID-19 patients (12%) developed SC-CIP.

SC-CIP is typically observed after sepsis in the setting of polytrauma, complicated surgery and other life threatening diseases [22]. The potential role of severe viral diseases in the development of SC-CIP is less well characterized, however SC-CIP was described in a case series as a complication of influenza A(H1N1) associated ARDS in 5 of 21 patients (24%)[23].

The pathophysiology of SC-CIP is not fully understood, however bile duct ischemia plays a critical role [12]. Unlike the hepatic parenchyma with its dual blood supply from the hepatic artery and the portal vein, the biliary tree obtains its blood supply exclusively from the hepatic arterial branches, the so called peribiliary vascular plexus. Therefore, the biliary epithelium is more suscpetible to changes in the arterial blood flow compared to the hepatic parenchyma [13,23-25] Supporting the hypothesis of bile duct ischemia, several predisposing factors for the development of SC-CIP have been elaborated. Severe hypotension with prolonged decrease in mean arterieal pressure (MAP)[22], initial need of large amounts of transfusions or colloids [22] and longer duration spent in prone position in patients with ARDS [23] have been suggested as trigger mechansims of SC-CIP. By contrast, the role of high dose catecholamine remains unclear, as Leonhardt and colleagues could not find any evidence that vasopressors play a crucial role in the pathogenesis of SC-CIP [22]. In addition to ischemic cholangiopathy, the concept of "toxic bile" has been suggested as another driver of SC-CIP. In animal models, disturbance of the finely-tuned balance between bile acid and protective mechanisms as consequence of alterations of the hepatobiliary transporter systems has been shown to result in sclerosing cholangitis [22]. Interestingly, in the group of severe cholestasis 7 of 9 patients were diabetics, which was significantly higher than in the group with mild cholestasis and 3 of 4 patients who developed SC-CIP had diabetes, which may suggest diabetes mellitus as a risk factor for a more severe cholestatic course in our cohort. However, the presence of diabetes was not different between the group of severe cholestasis and without cholestasis, therefore this finding has to be interpreted with caution. Also, the prevalence of diabetes was not significantly different between the COVID-19 cohort compared to the influenza cohort.

As mentioned above, none of our influenza patients developed SC-CIP even though these patients were even more critically ill reflected by higher SAPS II scores. Vasopressor use in turn was not significantly different between the two cohorts. Furthermore, it is mentionable that ketamine was used in all patients of

group 1 and 2. However, the potential role of ketamine as contributing factor in den development of SC-CIP as suggested in a recent report[26] cannot be additionally be elucidated since no clear association between the occurrence of SC-CIP and ketamine use is demonstrable. Lastly, it is noteworthy that all 4 SC-CIP patients had been treated using prone positioning whereas proning was not used for the ventilation of our influenza patients. However, due to the fact that proning for the treatment of severe ARDS has become standard of care[27,28] within the last decade it cannot sufficiently explain the striking occurrence of SC-CIP in our COVID-19 cohort.

Taken together, clinical characteristics cannot readily explain the occurrence of SC-CIP among COVID-19 patients but not in influenza patients. It is therefore tempting to speculate that there are COVID-19 associated factors that promote the development of SC-CIP such as COVID-19 associated vascular damage to the peribiliary plexus or direct damage to cholangiocytes. However, the limited number of patients precludes any firm conclusions to be drawn with respect to the incidence and pathogenesis of this complication in the context of COVID-19. Hepatic involvement in COVID-19 patients has been shown in several cohorts from China comprising mostly less severe infections of non-ICU patients [8,10,29,30]. Hepatocellular injury pattern among COVID-19 patients is found in up to 41% and ALT elevations are generally mild, defined as less than 5 times upper reference limit [10,29,31]. Cholestatic liver disease in COVID-19 patients appears to be less prevalent in these cohorts. A recently published review suggested that elevated ALP occurs in 2-5% of patients whereas increased GGT is found in 13-54% [31]. In contrast, our cohort-study reveals a high prevalence of cholestatic injury in critically ill COVID-19 patients. 59% had intrahepatic cholestasis during ICU stay including nine patients (27%) with severe cholestasis and jaundice.

Cholestasis in critically ill patients is mostly intrahepatic and occurs due to a variety of causes including SIRS, hypoxic hepatitis, drug-induced liver injury, and pertinent ICU therapy such as ventilatory support and total parenteral nutrition [32]. In line, patients with severe intrahepatic cholestasis in our study had significant longer ICU stay compared to the other groups. Furthermore, therapeutic interventions such as vasopressors use, proning, ECMO and RRT were significantly more frequent in these patients.

The postmortem histopathological findings in four patients impressively reflect the preterminal biochemical severity of cholestasis. The most striking finding in the two patients with preterminal high or rising bilirubin levels is the transmural necrosis of perihilar bile ducts. According to previous reports on bile duct lesions in the setting of liver transplantation, biliary casts, which presumably derive from necrotic bile ducts, and the subsequent formation of bile duct strictures have been reported as serious complications [33,34] and have been identified also histologically as ischemic-type biliary lesions [35]. The transmural necrosis in the two COVID-19 patients in our study therefore presumably represent the initial lesion that could lead to SC-CIP. It is tempting to speculate, that these patients could also have developed SC-CIP, if they had survived. Indeed, early histopathological findings in the liver biopsies of two COVID-19 survivors in our study who developed SC-CIP in the follow-up were highly suggestive of larger perihilar bile duct obstruction. This is in line with previously described histological changes in patients that develop SC-CIP[36,37].

Additionally to the well-known causes for ischemic bile duct damage in critically ill patients, there may be further harmful factors in COVID-19 patients. The fact that there were no unequivocal thrombi and/or endothelialitis in the small peribiliary vessels does not exclude them to occur on another level of the vasculature. In fact, several thrombi were detected in peripheral portal veins in both patients with transmural bile duct necrosis as well as in the patient with mesenteric ischemia. Interestingly, in the latter patient thrombi were even associated with endothelialitis - as it was described previously in COVID-19 patients [6]. Furthermore, also a mechanical component of vessel and/or bile duct kinking during prone positioning can not be excluded. Even though we did not perform additional analysis for the detection of viral particles, a direct viral damage to endothelial cells of the peribiliary plexus and/or cholangiocytes can not be excluded and may leed to further damage [5,38]. Overall, these data suggest, that multiple factors might damage the biliary tree (or the bile ducts) and may contribute to the surprisingly high prevalence of SC-CIP in severly ill COVID-19 patients.

The natural history of SC-CIP as sequelae of severe COVID-19 may be comparable to the dismal prognosis of SC-CIP in patients with severe burns or other causes [13,20] since two patients died after discharge from ICU and another SC-CIP patient had already been evaluated for liver transplantation because of deteriorating liver function.

In conclusion, we demonstrate the development of SC-CIP in 4 of 34 patients with severe COVID-19 but not in a comparative cohort of influenza A patients with severe ARDS. This entity therefore needs to be considered in the diagnostic work up of prolonged cholestasis. Whether disease specific factors of COVID-19 constitutes an additional risk factor for the development of SC-CIP cannot be proven and warrants further studies.

Abbreviations

AKI, acute kidney injury

ALT, alanine aminotransferase

ALP, alkaline phosphatase

AST, aspartate aminotransferase

ARDS, acute respiratory distress syndrome

BMI, body mass index

COVID-19, Coronavirus disease 2019

ECMO, extracorporeal membrane oxygenation

GGT; gamma-glutamyl-transferase

ICU, intensive care unit

INR, international normalized ratio

IQR, interquartile range

LFT, liver function tests

MAP, mean arterieal pressure

MRCP, magnetic resonance cholangiopancreatography

RRT, renal replacement therapy

SAPS II Score, Simplified Acute Physiology Score

SARS-Cov-2, severe acute respiratory syndrome coronavirus 2

SOFA Score, Sequential Organ Failure Assessment Score

SSC, secondary sclerosing cholangitis

SC-CIP, sclerosing cholangitis in critically ill patients

UDCA; Ursodeoxycholic acid

ULN, upper limit of normal.

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Characteristics	Overall	No Cholestasis Group 0	Cholestasis Group 1	Cholestasis Group 2	p-value
	(n=34)	(n=14; 41%)	(n=11; 32%)	(n=9; 27%)	
Age, years	60 [55-69]	63 [55-70]	59 [52-70]	59 [53-68]	0.809
Male sex	29 (85)	13 (93)	9 (82)	7 (78)	0.563
BMI, kg/m^2	28.0 [25.1-34.3]	29.0 [25.5-33.5]	28.0 [26.0-35.9]	27.0 [24.4-34.5]	0.653
Comorbidities					
Diabetes mellitus	15 (44)	7 (50)	1 (9)	7 (78)	0.007
Arterial hypertension	23 (68)	8 (57)	8 (73)	7 (78)	0.650
Adipositas	12 (35)	7 (50)	4 (36)	1 (11)	0.162
Chronic liver disease	0 (0)	0 (0)	0 (0)	0 (0)	1.000
Chronic lung disease	6 (18)	3 (21)	3 (27)	0 (0)	0.278
Chronic kidney disease	7 (21)	3 (21)	3 (27)	1 (11)	0.766
Immunosuppression†	6 (18)	1 (7)	4 (36)	1 (11)	0.166
Severity Scores					
SOFA (ICU admission)	8 [3-10]	4.5 [2.0-8.25]	10 [7-11]	8 [6-13.5]	0.021
SAPS II	33 [24-50]	25 [22-35]	42 [26-59]	44.0 [26-60]	0.035
LFT at admission					
AST, x ULN	0.9 [0.8-1.4]	0.9 [0.6-1.1]	1.9 [0.9-2.1]	0.9 [0.7-1.0]	0.012
ALT, x ULN	0.8 [0.5-1.2]	0.6 [0.5-1.0]	1.1 [0.9-2.1]	0.6 [0.5-0.9]	0.102
GGT, x ULN	1.2 [0.6-1.5]	0.9 [0.6-1.6]	1.3 [1.0-2.0]	1.2 [0.6-1.5]	0.402
ALP, x ULN	0.6 [0.4-0.7]	0.5 [0.4-0.7]	0.7 [0.4-0.7]	0.4 [0.4-0.7]	0.235
Total bilirubin, x ULN	0.4 [0.3-0.6]	0.5 [0.2-0.6]	0.5 [0.2-0.6]	0.3 [0.3-0.4]	0.392
INR	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	0.181
Peak LFT					
AST, x ULN	4.0 [2.5-11.0]	2.8 [1.5-3.6]	4.1 [2.5-16]	13.4 [8.3-100.5]	<0.001
ALT, x ULN	3.7 [2.3-8.1]	2.4 [2.0-3.6]	5.5 [1.7-8.1]	12.4 [7.3-55.6]	0.001
GGT, x ULN	7.9 [4.9-26.5]	4.5 [2.0-6.5]	9.4 [6.0-14.5]	36.9 [26.6-54.9]	<0.001
ALP, x ULN	1.8 [1.0-3.5]	0.9 [0.5-1.0]	2.1 [1.8-2.9]	9.1 [3.8-18.1]	<0.001
Total bilirubin, x ULN	1.0 [0.5-2.6]	0.5 [0.4-0.8]	1.0 [0.6-1.6]	8.0 [3.5-13.5]	<0.001
INR	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.1 [1-2.2]	0.378
LFT at discharge / death					
AST, x ULN	0.9 [0.6-2.1]	0.7 [0.5-0.9]	1.0 [0.9-1.6]	2.5 [0.7-3.7]	0.032
ALT, x ULN	1.2 [0.8-2.3]	1.0 [0.7-1.6]	1.2 [0.8-3.2]	2.0 [1.0-2.8]	0.302
GGT, x ULN	4.8 [2.2-11.2]	1.7 [1.2-3.7]	5.5 [3.0-10.0]	11.9 [5.4-30.4]	0.001
ALP, x ULN	1.4 [0.9-3.4]	0.7 [0.4-0.9]	1.7 [1.2-2.0]	5.4 [2.5-7.4]	<0.001
Total bilirubin, x ULN	0.4 [0.2-1.6]	0.3 [0.2-0.4]	0.3 [0.1-1.2]	6.0 [0.4-9.5]	0.012
INR	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	1.0 [1.0-1.0]	0.734
Treatments at ICU					
Vasopressors	27 (79)	8 (57)	11 (100)	8 (89)	0.018
Mechanical ventilation	31 (91)	11 (79)	11 (100)	9 (100)	0.102
Proning	23 (68)	6 (43)	8 (73)	9 (100)	0.012

Nitric Oxide	5 (15)	0 (0)	1 (9)	4 (44)	0.007
ECMO	7 (21)	0 (0)	3 (27)	4 (44)	0.028
RRT	15 (44)	2 (14)	7 (64)	6 (55)	0.013
Parenteral nutrition	5 (14)	0 (0)	2 (18)	3 (27)	0.065
Outcomes					
Nosocomial Infection	18 (53)	6 (43)	6 (55)	6 (67)	0.516
Bacteremia	9 (27)	1 (7)	3 (27)	5 (56)	0.045
Sepsis	10 (29)	3 (21)	3 (27)	4 (44)	0.565
Septic shock	12 (35)	2 (14)	6 (55)	4 (44)	0.128
AKI	18 (53)	4 (29)	8 (73)	6 (67)	0.059
ARDS	28 (82)	9 (64)	10 (91)	9 (100)	0.080
ICU days	17 [8-36]	9.5 [3.8-18.3]	16 [8-30]	51 [25-86.5]	0.002
Overall Mortality	10 (29)	1 (7)	4 (36)	5 (56)	0.043
COVID-19 specific medication					
Hydroxychloroquine	21 (62)	6 (43)	9 (82)	3 (75)	0.065
Remdesivir	6 (18)	2 (14)	2 (18)	1 (11)	1.000
Lopinavir/Ritonavir	5 (15)	1 (7)	2 (18)	2 (22)	0.579
Tocilizumab	1 (3)	1 (7)	0 (0)	0 (0)	1.000

Table 1: Clinical and laboratory characteristics of the COVID-19 cohort. Continuous variables are expressed as median and interquartile range (IQR). Categorical variables are expressed as n (%). Statistical Analysis: Kruskal-Wallis and Fisher's exact test as appropriate. AKI, acute kidney ; ALT, alanine aminotransferase; ALP, alkaline phosphatase, AST, aspartate aminotransferase; ARDS, acute respiratory distress syndrome; BMI, body mass index; GGT; gamma-glutamyl-transferase; ICU, intensive care unit; INR, international normalized ratio; LFT, liver function tests; RRT, renal replacement therapy; SAPS II Score, Simplified Acute Physiology Score; SOFA Score, Sequential Organ Failure Assessment Score; ULN, upper limit of normal. †Immunosuppression was defined as any of the following: hematologic malignancy, Human Immunodeficiency Virus, prescribed immunosuppressive medication.

Characteristics	Overall (n=68)	COVID-19 (n=34)	Influenza A (n=34)	p-value
Age, years	59 [53-68]	60 [55-69]	58 [49-67]	0.164
Male sex	48 (71)	29 (85)	19 (56)	0.017
BMI, kg/m^2	27.3 [23.9-31.1]	28.0 [25.1-34.3]	25.9 [23.0-28.9]	0.050
Comorbidities				
Arterial hypertension	35 (51)	23 (68)	12 (35)	0.015
Diabetes mellitus	23 (34)	15 (44)	8 (24)	0.124
Chronic liver disease	4 (6)	0 (0)	4 (12)	0.122
Chronic lung disease	20 (29)	6 (18)	14 (41)	0.062
Chronic kidney disease	15 (22)	7 (21)	8 (24)	1.000
Immunosuppression †	14 (21)	6 (18)	8 (24)	0.764
Severity Scores				
SOFA (ICU admission)	9 [6-11]	8 [3-10]	9 [8-12]	0.025
SAPS II	44 [30-57]	33 [24-50]	53 [40-60]	0.002
PaO$_2$/ FiO$_2$, mmHg	99 [75-165]	105 [84-170]	93 [68-140]	0.130
LFT at admission				
AST, x ULN	1.1 [0.8-1.9]	0.9 [0.8-1.4]	1.5 [1.0-2.9]	0.008
ALT, x ULN	0.9 [0.5-1.4]	0.8 [0.5-1.2]	1.0 [0.6-1.6]	0.213
GGT, x ULN	1.2 [0.7-1.6]	1.2 [0.6-1.5]	1.3 [0.8-2.0]	0.582
ALP, x ULN	0.6 [0.4-0.8]	0.6 [0.4-0.7]	0.7 [0.5-1.2]	0.004
Total bilirubin, x ULN	0.4 [0.2-0.6]	0.4 [0.3-0.6]	0.4 [0.2-0.9]	0.610
INR	1.1 [1.0-1.2]	1.0 [1.0-1.0]	1.2 [1.1-1.4]	<0.001
Treatments at ICU				
Vasopressors	59 (87)	27 (79)	32 (94)	0.152
Mechanical ventilation	60 (88)	31 (91)	29 (85)	0.707
Proning	30 (44)	23 (68)	7 (21)	<0.001
Parenteral nutrition	10 (15)	5 (15)	5 (15)	1.000
ECMO	17 (25)	7 (21)	10 (29)	0.575
Complications				
Septic shock	30 (44)	12 (35)	15 (53)	0.222
ARDS	61 (90)	28 (81)	33 (97)	0.110
Acute Kidney Injury	39 (57)	18 (53)	21 (62)	0.624
Cholestasis				0.009
No	40 (59)	14 (41)	26 (76)	
Mild	17 (25)	11 (32)	6 (18)	
Severe	11 (16)	9 (27)	2 (6)	
SSC	4 (6)	4 (12)	0 (0)	
Outcome				
ICU days	15 [7-30]	17 [8-36]	13 [6-24]	0.414
Hospital mortality	19 (28)	10 (29)	12 (35)	0.280

Table 2: Patient characteristics of the two cohorts at admission to ICU. Data are presented as median [interquartile range] or counts (percentages) as appropriate. Statistical analysis: Kruskal-Wallis and Chi-Square test as appropriate. ALT, alanine aminotransferase. ALP, alkaline phosphatase. AST, aspartate aminotransferase. ARDS, acute respiratory distress syndrome. BMI, body mass index. COVID-19, Coronavirus disease 2019. ECMO, extracorporeal membrane oxygenation. GGT; gamma-glutamyl-transferase. ICU, intensive care unit. INR, international normalized ratio. BMI, body mass index. RRT, renal replacement therapy. SAPS II, Simplified Acute Physiology Score. SOFA, Sequential Organ Failure Assessment Score. SSC, secondary sclerosing cholangitis. †Immunosuppression was defined as any of the following: hematologic malignancy, Human Immunodeficiency Virus, prescribed immunosuppressive medication.

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4
Age, years	59	67	54	64
Sex	M	M	F	M
BMI, kg/m^2	28.0	24.0	24.7	24.7
Comorbidities				
Diabetes mellitus	Yes	Yes	Yes	No
Adipositas	No	No	No	No
Chronic liver disease	No	No	No	No
Chronic lung disease	No	No	No	No
Chronic kidney disease	No	No	No	No
Severity Scores				
SOFA (ICU admission)	15	12	7	14
SAPS II	72	45	28	70
LFT at admission				
AST, x ULN	0.96	0.62	0.77	0.92
ALT, x ULN	0.54	0.36	0.86	0.62
GGT, x ULN	0.60	0.25	1.55	0.62
ALP, x ULN	0.25	0.58	0.58	0.39
Total bilirubin, x ULN	0.38	0.24	0.29	0.57
INR	1.0	1.0	1.0	1.0
Peak LFT				
AST, x ULN	28.70	13.44	9.26	33.14
ALT, x ULN	19.84	7.26	12.37	23.04
GGT, x ULN	55.97	28.15	85.13	50.52
ALP, x ULN	21.26	18.81	17.30	12.85
Total bilirubin, x ULN	26.05	8.05	3.81	17.43
INR	1.0	1.0	1.0	2.2
Time form ICU admission to first rise of ALP (days)	20	10	10	6
Time from ICU admission to diagnosis of SSC (days)	70	74	153	75
Treatments at ICU				
Vasopressors	Yes	Yes	Yes	Yes
Mechanical ventilation	Yes (43 days)	Yes (20 days)	Yes (55 days)	Yes (28 days)
Proning	Yes (10 days)	Yes (6 days)	Yes (10 days)	Yes (11 days)
Nitric Oxide	No	No	Yes	Yes
ECMO	No	Yes	Yes	No
RRT	Yes	Yes	No	Yes
Parenteral nutrition	Yes	No	No	No
Ketamine Sedation	Yes (16 days)	Yes (5 days)	Yes (23 days)	Yes (14 days)
Anticoagulation	Heparin	Heparin	Heparin	Heparin
Outcomes				

Nosocomial Infection	Yes	Yes	No	No
Septic shock	No	No	Yes	Yes
AKI	Yes	Yes	No	Yes
ARDS	Yes	Yes	Yes	Yes
ICU days	51	98	78	88
ICU mortality	No	No	No	No
Listed for liver transplant	Yes	n.a.	No	n.a.
COVID-19 specific medication	Hydroxy-chloroquine	Hydroxy-chloroquine	Hydroxy-chloroquine, Lopinavir / Ritonavir	None
Other Medication				
UDCA	Yes	Yes	Yes	Yes
Steroids	No	No	No	No
MRCP with typical findings of SC-CIP	Yes	Yes	Yes	Yes
Follow-up after hospital discharge	Last follow up 7 month 3 weeks after discharge from ICU, liver cirrhosis Child B, MELD 17, deeply jaundiced (Bilirubin 217 ymol/l), on the transplant waiting list	Exitus letalis 55 days after ICU discharge (80 days after SSC diagnosis) due to respiratory failure (pulmonary infection)	Last follow up 9 month and 2 weeks after discharge from ICU, compensated liver function, persistenly marked increased ALP and GGT	Exitus letalis 14 days after ICU discharge (26 days after SSC diagnosis) due to sepsis / pulmonary infection

Table 3: **Patient characteristics of the four individuals developing SC-CIP (sclerosing cholangitis in critically ill patients).** AKI, acute kidney injury; ALT, alanine aminotransferase; ALP, alkaline phosphatase, AST, aspartate aminotransferase; ARDS, acute respiratory distress syndrome; BMI, body mass index; GGT; gamma-glutamyl-transferase; ICU, intensive care unit; INR, international normalized ratio; LFT, liver function tests; MRCP, magnetic resonance cholangiopancreatography; RRT, renal replacement therapy; SAPS II Score, Simplified Acute Physiology Score; SOFA Score, Sequential Organ Failure Assessment Score; SSC, secondary sclerosing cholangitis; UDCA, Ursodeoxycholic acid; ULN, upper limit of normal.

Figure Legends

Figure 1: Study flow chart. Death refers to mortality during hospital stay. SSC, secondary sclerosing cholangitis.

Figure 2: ICU characteristics according to cholestasis groups of patients with COVID-19 infection.
A: ICU days among different groups. **B:** SAPS II Score among different groups. Median (black bar), interquartile range (blue box) and 95% confidence interval (Whiskers) are indicated. **C:** ICU treatments among different groups (percentages of patients receiving in each group). Statistical analysis: A/B: Mann-Whitney U test. C: Fisher's exact. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ICU, Intensive care unit; SAPS II Score, Simplified Acute Physiology Score; ns, not significant.

Figure 3: Peak ALT x ULN and outcome of each individual. Death refers to mortality during follow-up time. ALT, alanine aminotransferase; ULN, upper limit of normal, SSC, secondary sclerosing cholangitis

Figure 4. **Representative findings in liver biopsies from patients that developed SC-CIP (A) – (D) and in autopsy livers (E) – (F)**. **(A)** Portal tract with edema, mixed portal inflammation and severe bile duct damage with ductular reaction (H&E; scale bar 100 μm; insert: CK7-immunohistochemistry; scale bar 100 μm). **(B)** Ductular (black arrowhead) and canalicular (white arrowheads) cholestasis (H&E; scale bar 50 μm). **(C)** Lobular bile infarcts and hepatocellular cholestasis (H&E; scale bar 50 μm). **(D)** Pericellular fibrosis around portal tracts (black arrowheads) and central vein (white arrowhead) (Sirius red; scale bar 200 μm). **(E)** Transmural necrosis of perihilar bile ducts in patients with preterminally high bilirubin levels (H&E; scale bar 500 μm; insert scale bar 100 μm). **(F)** Perihilar bile ducts with damage and detachment of the epithelium but viable walls in patients with mild cholestasis (H&E; scale bar 500 μm; insert scale bar 100 μm). In **(E)** and **(F)** viable blood vessel walls, viable peripheral nerves and viable hepatocytes are visible.

Figure 5: Representative MRCP image of a SC-CIP patient in our cohort showing diffuse irregularities of the bile ducts with dilatations and strictures. MRCP, magnetic resonance cholangiopancreatography; SC-CIP, sclerosing cholangitis in critically ill patients.
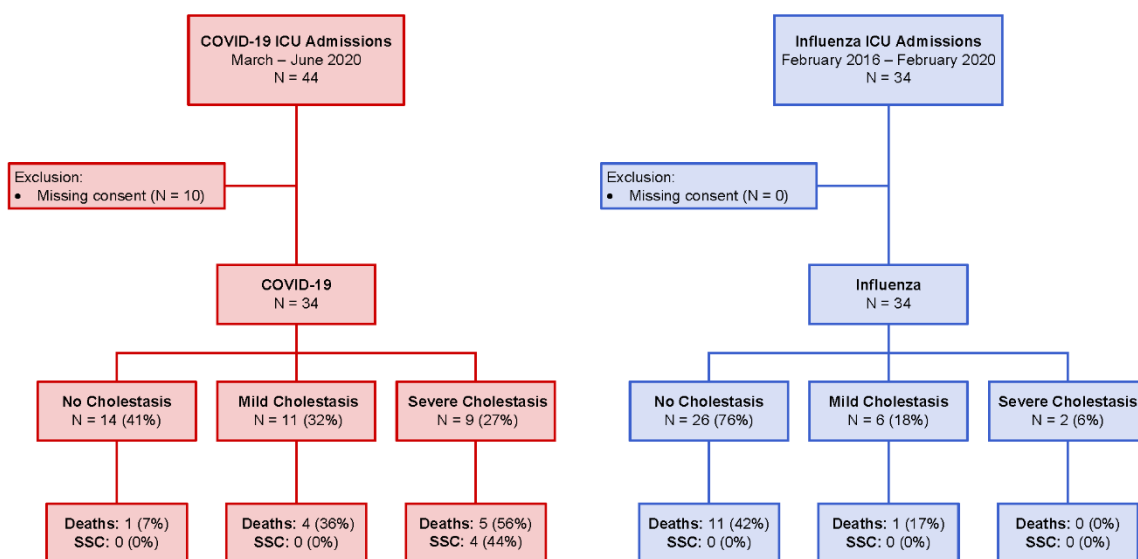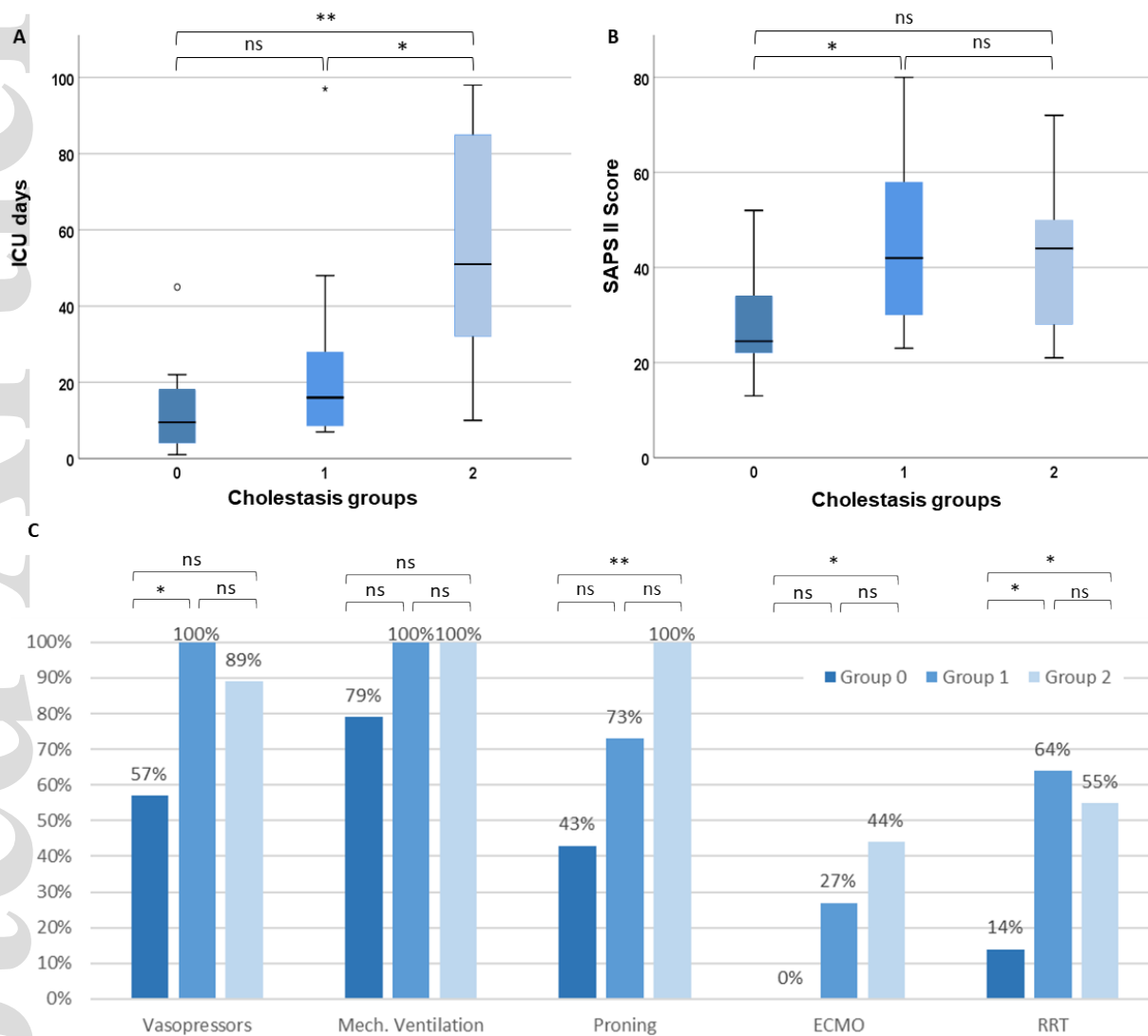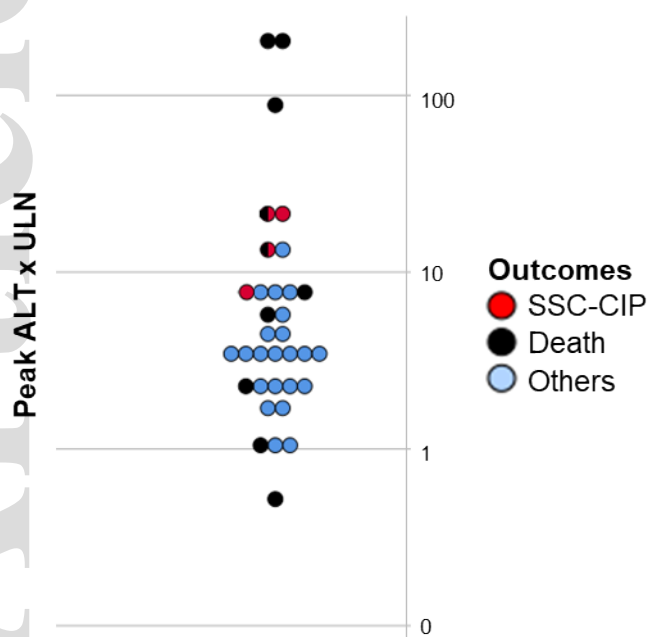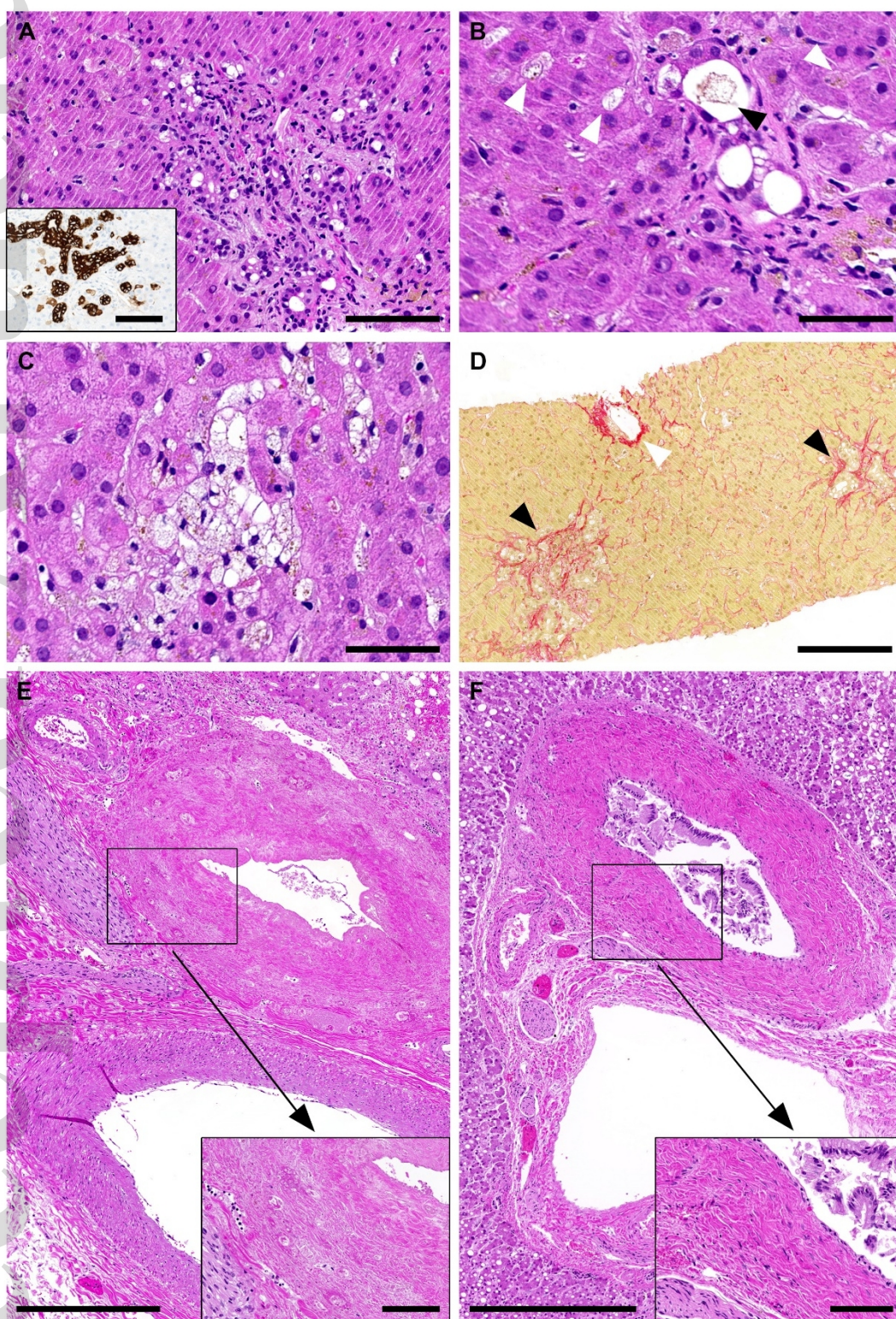
Figures

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5